Chinese Chemical Letters 32 (2021) 672–675

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

# Organocatalytic asymmetric [3 + 3] annulation of isatin *N,N'*-cyclic azomethine imines with enals: Efficient approach to functionalized spiro *N*-heterocyclic oxindoles

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ARTICLE INFO

*Article history:*
Received 16 May 2020
Received in revised form 5 June 2020
Accepted 8 June 2020
Available online 9 June 2020

*Keywords:*
Chiral secondary amine
[3 + 3] Annulation
Azomethine imines
Spiro *N*-heterocyclic oxindole
Asymmetric synthesis

ABSTRACT

An unprecedented chiral secondary amine-catalyzed [3 + 3] annulation of isatin *N,N'*-cyclic azomethine imines with *α,β*-unsaturated aldehydes was developed. This strategy allowed the construction of structurally novel spiro *N*-heterocyclic oxindole derivatives in good yields (up to 91%) and good to excellent enantioselectivities (up to >99% *ee*), albeit with modest diastereoselectivities (up to 3.1:1 dr).


Optically active 3,3-disubstituted oxindoles are identified as privileged structures in natural products and pharmaceuticals [1]. Among those structures, spiro *N*-heterocyclic oxindoles fused with a five- or six-membered ring system at the C3-position have drawn considerable attention from both synthetic and medicinal chemists because it contains two pharmaceutical and biological characteristics of both heterocycle and oxindole motifs [2].

Given the significance of such skeleton, several elegant and efficient approaches have been developed for constructing 3-spiro *N*-heterocyclic oxindoles in the last ten years [3–5]. Among the reported methods, the asymmetric 1,3-dipolar cycloaddition of *N*, *N'*-cyclic azomethine imines are one of the most effective and direct approaches for the construction of chiral 3-spiro heterocyclic oxindoles [6]. In this context, Wang and Feng group independently identified the azomethine imines as a versatile and robust building block in the asymmetric 1,3-dipolar cycloaddition for the construction of 3-spiroheterocyclicoxindoles. Despite the elegant work, the substrates are still limited: 1) azomethine imines are prepared by the condensation of pyrazolidin-3-one with aldehydes; 2) the dipolarophiles are limited to 2-oxoindolin-3-ylidene (Scheme 1) [7,8].

Recently, Wang and co-workers designed a new isatin *N,N'*-cyclic azomethine imine synthon, which performed unexpected reactivity in the [3 + 2] annulation and Michael addition with electron-deficient alkenes (Scheme 2) [9,10]. However, the asymmetric version of the above protocol was not achieved, or only poor enantioselectivity was obtained. In view of the limitations of current methods and the importance of 3-spiro heterocyclic oxindoles, we envisaged that chiral 3-spiro heterocyclic oxindoles could be obtained *via* the asymmetric annulation of isatin *N,N'*-cyclic azomethine imines with enals in the presence of chiral secondary amine catalysts (Scheme 2) [11].

In order to verify our assumption, we investigated the asymmetric annulation between model substrates isatin *N,N'*-cyclic azomethine imine **1a** and cinnamaldehyde **2a** in the presence of TMS-protected secondary amine catalyst **C1** (Fig. 1). Surprisingly, an unexpected C-*N*-*N* [3 + 3] annulation process was observed, which was different from previously reported reaction mode, and corresponding product **3aa** was obtained in good yield (72%), modest diastereoselectivity (1.2:1) and high enantioselectivity (87%/80% *ee*) (Table 1, entry 1). Encouraged by this promising result, various chiral amine catalysts (**C2**–**C5**, Fig. 1) were screened (entries 2–5). Gratifyingly, bulkier amine catalyst **C2** exhibited the optimal reaction outcome, both yield (81%) and stereoselectivity (1.7:1 dr, 91%/90% *ee*) were improved (entry 2).

Subsequently, by varying the base for this reaction, no better results could be obtained compared with $Et_3N$ (Table 2, entries 1–6). Then, the effect of solvents was tested. When using $CH_2Cl_2$ as

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https://doi.org/10.1016/j.cclet.2020.06.010
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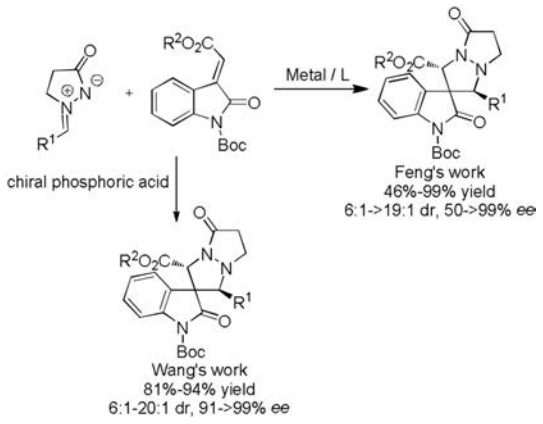
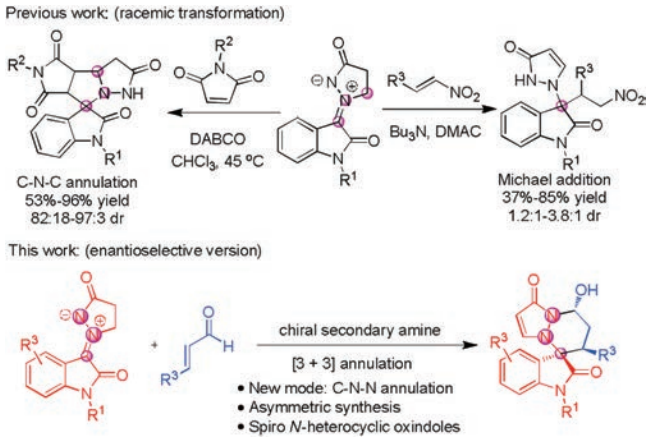



**Scheme 1.** Asymmetric construction of spiro *N*-heterocyclic oxindole derivatives by *N,N'*-cyclic azomethine imines.




**Scheme 2.** Synthetic applications of isatin *N,N'*-cyclic azomethine imine.

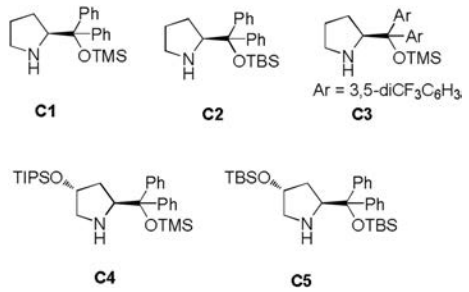



**Fig. 1.** Chiral secondary-amine catalysts investigated in this reaction.

solvent, the yield was slightly reduced (80%), but the stereoselectivity was significantly improved (1.9:1 dr, 96%/95% *ee*) (entry 7). DMF reduced the reaction time greatly (12 h), but the yield (52%) and stereoselectivity (1:1.5 dr, 66%/76% *ee*) were not ideal (entry 13). Other solvents, such as $CH_3CN$, $CH_3OH$, THF, $Et_2O$ and toluene led to a significant decrease in reactivity due to the reduced solubility of isatin *N,N'*-cyclic azomethine imine **1a** (entries 8–12). In addition, investigation of the reaction temperature showed that $CH_2Cl_2$ at 0 °C gave better result (82% yield, 2.1:1 dr, 98%/96% *ee*) in comparison with $CHCl_3$ (entries 14 and 15).

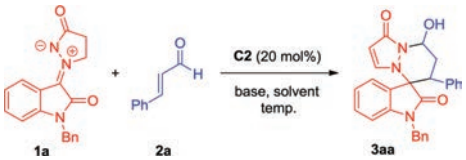
With the optimal conditions in hand, the substrate scope of isatin *N,N'*-cyclic azomethine imines and *α,β*-unsaturated aldehydes was subsequently investigated. Firstly, various protecting groups on substituted isatin *N,N'*-cyclic azomethine imines were

**Table 1**
Screenings of catalysts.[a]


| entry | **cat** (mol%) | *t* (h) | yield (%)[b] | dr[c] | *ee* (%)[d] |
|---|---|---|---|---|---|
| 1 | **C1** (20) | 28 | 72 | 1.2:1 | 87/80 |
| 2 | **C2** (20) | 28 | 81 | 1.7:1 | 91/90 |
| 3 | **C3** (20) | 28 | 76 | 1.3:1 | 80/80 |
| 4 | **C4** (20) | 28 | 82 | 2.4:1 | 83/81 |
| 5 | **C5** (20) | 32 | 80 | 3.4:1 | 85/84 |

[a] Unless otherwise stated, reactions were carried out with 0.10 mmol of **1a**, 0.15 mmol of **2a** and $Et_3N$ (20 mol%) in 1.0 mL of $CHCl_3$ at room temperature.
[b] Isolated yields.
[c] Determined by crude $^1H$ NMR spectroscopy.
[d] Determined by chiral HPLC analysis.

**Table 2**
Optimization of reaction conditions.[a]

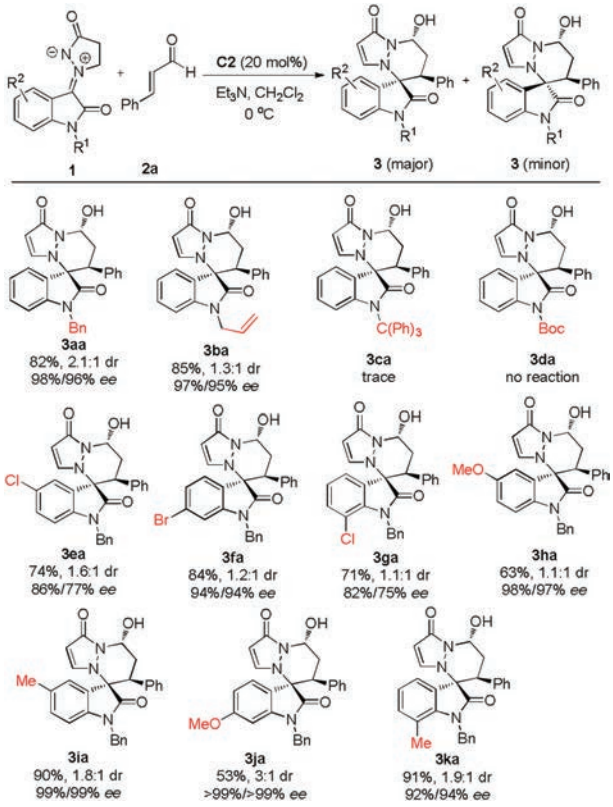



| Entry | Base | Solvent | *t* (h) | Yield (%)[b] | dr[c] | *ee* (%)[d] |
|---|---|---|---|---|---|---|
| 1 | DIPEA | $CHCl_3$ | 48 | 60 | 1.6:1 | 85/83 |
| 2 | $K_2CO_3$ | $CHCl_3$ | 40 | 65 | 1.4:1 | 69/81 |
| 3 | DMAP | $CHCl_3$ | 48 | 58 | 1.5:1 | 74/94 |
| 4 | DABCO | $CHCl_3$ | 40 | 68 | 1.2:1 | 88/87 |
| 5 | DBU | $CHCl_3$ | 12 | 55 | 0.9:1 | 58/21 |
| 6 | $Et_3N$ | $CHCl_3$ | 28 | 82 | 1.7:1 | 91/90 |
| 7 | $Et_3N$ | $CH_2Cl_2$ | 24 | 80 | 1.9:1 | 96/95 |
| 8 | $Et_3N$ | toluene | 96 | – | – | – |
| 9 | $Et_3N$ | $CH_3CN$ | 96 | trace | – | – |
| 10 | $Et_3N$ | $CH_3OH$ | 96 | – | – | – |
| 11 | $Et_3N$ | THF | 96 | trace | – | – |
| 12 | $Et_3N$ | $Et_2O$ | 96 | – | – | – |
| 13 | $Et_3N$ | DMF | 12 | 52 | 1:1.5 | 66/76 |
| 14[e] | $Et_3N$ | $CHCl_3$ | 48 | 82 | 2.3:1 | 95/94 |
| 15[e] | $Et_3N$ | $CH_2Cl_2$ | 32 | 82 | 2.1:1 | 98/96 |

[a] Unless otherwise stated, reactions were carried out with 0.10 mmol of **1a**, 0.15 mmol of **2a**, **C2** (20 mol%) and base (20 mol%) in 1.0 mL of solvent at room temperature.
[b] Isolated yields.
[c] Determined by crude $^1H$ NMR spectroscopy.
[d] Determined by chiral HPLC analysis.
[e] Reaction conducted at 0 °C.

explored with cinnamaldehyde **2a** (Scheme 3). *N*-Allyl protected substrate **1b** afforded the [3 + 3] cycloadduct in good yield with excellent enantioselectivity (85%, 1.3:1 dr, 97%/95% *ee*). Due to the influence of high steric hindrance and poor solubility, *N*-C(Ph)$_3$ protected **1c** only afforded the trace amount of product. On the other hand, the electron-withdrawing group Boc-protected **1d** showed no reactivity. Then various electron-donating or electron-withdrawing groups at 5-, 6-, 7-positions on the indole ring were also tolerated, the corresponding products could be obtained in good yields, while electron-withdrawing substitutions on the indole ring gave lower yield and decreased enantioselectivity compared with electron-donating substitutions (**3ea**–**3ka**).

Subsequently, the potential of this [3 + 3] annulation with a variety of *α,β*-unsaturated aldehydes was further explored (Scheme 4). The reaction all proceeded smoothly, good yields

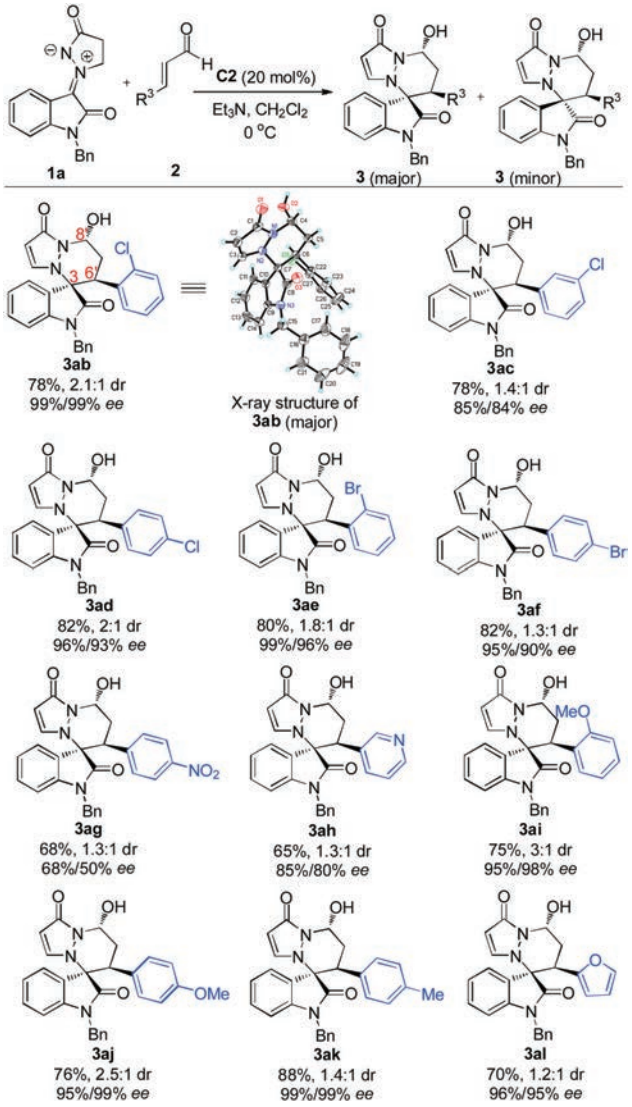



**Scheme 3.** Scope of isatin *N,N'*-cyclic azomethine imines **1**. General reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), **C2** (0.04 mmol), $Et_3N$ (0.04 mmol), $CH_2Cl_2$ (2.0 mL), 0 °C. Isolated yields for two diastereomers; dr values were determined by $^1H$ NMR spectroscopy; *ee* values were determined by chiral HPLC analysis.

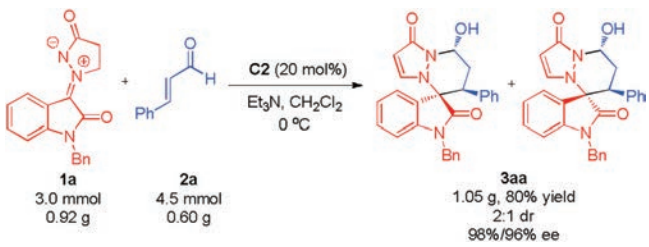
and moderate to excellent enantioselectivities were obtained with the aryl rings bearing electron-withdrawing Cl, Br, $NO_2$ or -donating Me, OMe substitutions (**3ab**–**3ag**, **3ai**–**3ak**). Furthermore, heteroaromatic aldehydes such as pyridyl and furyl were also tolerated under optimal conditions (**3ah**, **3al**). In addition, the absolute configuration of **3ab** (major diastereoisomer) was determined as (3*R*, 6'*S*, 8'*R*) by X-ray crystallographic analysis, and the absolute configuration of minor diastereoisomer was determined as (3*S*, 6'*S*, 8'*R*) by X-ray crystallographic analysis (for details see the Supporting information). Notably, aromatic aldehyde **2g** bearing *para*-nitryl substituent and heteroaromatic aldehyde **2h** bearing 3-pyridyl substituent merely delivered moderate enantioselectivities (68%/50% *ee*, 85%/80% *ee*), presumably because the strong electron-withdrawing group obviously enhanced the reaction activities. It should be mentioned that in all cases except **3ah** and **3ai**, the corresponding diastereoisomers can be easily separated by flash column chromatography.

To further demonstrate the synthetic utility of this process, the [3 + 3] annulation between **1a** and **2a** was carried out on a gram scale, and compound **3aa** was obtained in 80% yield, 2:1 dr and 98%/96% *ee* (Scheme 5).

A plausible reaction pathway was proposed to rationalize the formation of product **3aa** (Scheme 6). According to Wang's previous report [9] key intermediate **III** is formed through the resonance of **1a** in the presence of $Et_3N$, and imine **IV** is formed through the condensation reaction between enal **2a** and catalyst **C2** at the same time. Then enantioselective Michael addition of intermediate **III** to chiral imine **IV** occurs, and generates the intermediate **VI** with a double bond shift. Finally, the target product **3aa** is afforded *via* the hydrolysis/intramolecular cyclization.

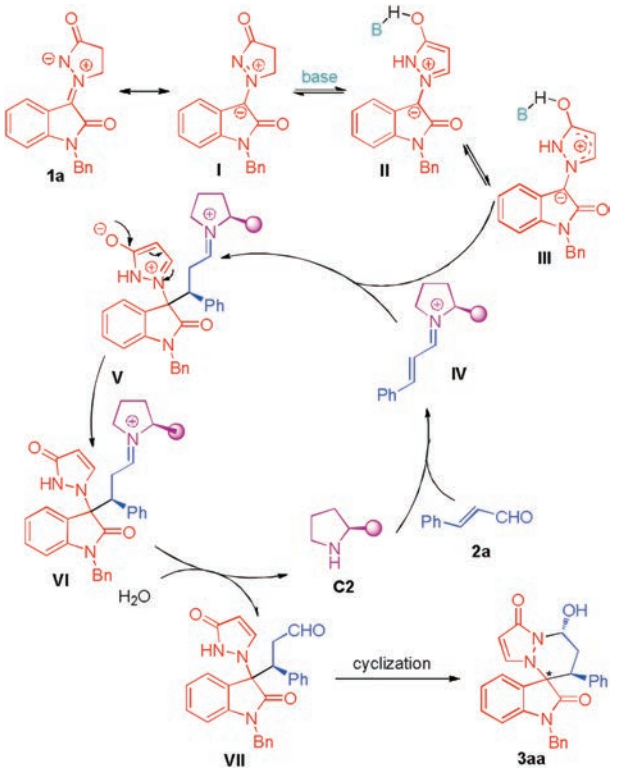



**Scheme 4.** Scope of $\alpha,\beta$-unsaturated aldehydes **2**. General reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), **C2** (0.04 mmol), $Et_3N$ (0.04 mmol), $CH_2Cl_2$ (2.0 mL), 0 °C. Isolated yields for two diastereomers; dr values were determined by $^1H$ NMR spectroscopy; *ee* values were determined by chiral HPLC analysis.




**Scheme 5.** Gram-scale experiments.

In summary, we have presented the first example of enantioselective C-*N*-*N* [3 + 3] annulation of isatin *N,N'*-cyclic azomethine imines with $\alpha,\beta$-unsaturated aldehydes by employing the chiral secondary amine as catalyst. A wide range of highly substituted spiro *N*-heterocyclic oxindole derivatives were synthesized in good yields (up to 91%) and good to excellent enantioselectivities (up to >99% *ee*). The present approach is a supplement to the previous methods for the diversity-oriented synthesis of biologically crucial




**Scheme 6.** Proposed reaction pathway.

enantioenriched spiro *N*-heterocyclic oxindole derivatives in high efficiency.

## Declaration of competing interest

The authors declare no competing financial interest.

## Acknowledgments

This work is supported by the National Natural Science Foundation of China (No. 21572053) and Opening Project of Zhejiang Provincial Preponderant and Characteristic Subject of Key University (Traditional Chinese Pharmacology), Zhejiang Chinese Medical University (No. ZYAOX2018029).

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.06.010.

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